VIEWPOINT

Interfering with healing: the benefits of intervention during acute myocardial infarction

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Early thrombolysis and low dose aspirin reduce mortality from myocardial infarction by about 25%,[1] and in combination the two drugs have an additive effect, reducing mortality by 45%.[2] This reduction is maintained for up to 12 years after the event and the survival curves of placebo treated patients are parallel to those of the treated groups, showing that there is no additional long term effect of active treatment.[2–4] The benefit is simply a reduced case fatality rate at the time of the event. In this paper we discuss a hypothetical explanation for these observational data, based on current understanding of the pathophysiological processes during infarction and the effects of reperfusion therapy.

Although postmortem examinations are limited, there is no single cause for the observed benefit but a general reduction in mortality and complications across the board.[5–7] That infarct size is reduced by thrombolytic treatment is seen by cumulative measurements of cardiac enzyme release and left ventricular function is better in patients treated early.[8–9] Most commentators have attributed the reduction in mortality to preservation of left ventricular function by early reperfusion by way of a number of theoretical mechanisms (table 1).[10–12] However, the absolute difference in left ventricular ejection fraction between groups treated with placebo and those treated by thrombolysis is small.[13] Moreover, mortality is reduced in patients treated late despite little evidence of a reduction in infarct size and is seen in patients with both inferior and anterior infarction, yet inferior infarcts have little effect on left ventricular function.[1] Most important, if the benefit of thrombolytic treatment were a result of a reduction of infarct size with consequent preservation of left ventricular function, better healing, or remodelling, then this effect would be more obvious in the recovery phase after acute myocardial infarction, showing an increasing benefit in patients given thrombolytic therapy. How does aspirin have the same size of mortality benefit as thrombolysis when it has no measurable effect on left ventricular function or infarct size?

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Table 1 Postulated mechanisms for reduced mortality after thrombolysis by improvements in left ventricular function

Reduction in left ventricular dilatation
Reduction in infarct expansion
Preservation of left ventricular geometry
Inhibition of aneurysm formation
Preservation of peri-infarct myocytes
Maintenance by blood in the coronary vessels of a vascular skeleton to prevent dilation
Decrease in type III collagen with more rapid healing
Increase in type I collagen that is more resistant to expansion
Promotion of fibroblasts conversion to myofibroblasts that are capable of contraction
Improved collateral flow

Acute inflammation—damage during repair

During myocardial infarction, when endothelial disruption, thrombotic activation, and prolonged ischaemia are established, an acute inflammatory response is perpetuated by the release of mediators of chemoattraction and adhesion molecules. Activated neutrophils migrate, producing oxygen free radicals, which increase myocyte damage. Adherent platelets and lymphocytes release cytokines and growth factors, further amplifying the inflammatory response. This cascade of chemical changes and inflammatory cell activation increases the myocardial cell damage caused by the original ischaemic insult and exacerbates the functional deficit of decreased myocyte contractility. Later healing begins by fibrosis. This may be considered a beneficial outcome of the inflammatory response that, by leading to scar formation, protects against cardiac rupture.

Inflammatory markers are positively correlated with adverse outcomes and clinical and haemodynamic measures of left ventricular dysfunction. The concentration of plasma C reactive protein (CRP) is an independent predictor of death and subsequent complications in patients admitted after acute infarction.[14] Cytokine activity is increased at the site of plaque rupture and throughout the damaged myocardium,[15] with spillover into the circulation. Serum interleukin 6 concentration increases acutely after myocardial infarction and correlates with CRP concentrations.[16] Tumour necrosis factor (TNF) concentration also rises after infarction, correlating with infarct size and left ventricular dysfunction.[17 18] There is evidence that these mediators of inflammation, as well as being indirect markers of infarct size, are directly detrimental to the myocardium[19] and that specific inhibition of these mediators limits the size of experimental infarction.[18]

Do acute interventions interrupt the inflammatory response?

Opening of the infarct related artery by thrombolysis interrupts the infarction process by relieving ischaemia and may allow salvage of

some myocytes not yet dead. This effect is not dependent on the presence of a persistently patent coronary artery throughout the healing process, although late follow up data show that an open infarct related artery confers a better long term prognosis.[20] In placebo controlled trials, there is little difference in the frequency of open infarct related arteries between placebo and thrombolytic groups by three weeks after the event.[4] Thus, if opening up the infarct related artery is important, it is the early effect that is beneficial. Successful reperfusion therapy also suppresses the acute inflammatory response, as evidenced by reduced CRP and TNF concentrations in humans[19 21] and reduced myocardial cytokine expression in rats.[15]

The clinical marker of inflammation following acute myocardial infarction is pericarditis and, in two early trials, the frequency of this complication in patients given thrombolytic treatment was about half that with placebo (GISSI (Studio della streptochinasi nell'infarto miocardico) 6.5% *v* 12.1%[5]; AIMS (APSAC intervention mortality study) 6.9% *v* 15.5%[6]). Aspirin was not routinely used in these trials and was given to only 13–15% of patients in GISSI and 2–3% in AIMS. The reduction in the frequency of pericarditis was greater than any other clinical effect seen in these trials.

Although aspirin reduces platelet activation, which may aid thrombolysis by reducing reocclusion, drugs that are more powerful antiplatelet agents are no better in secondary prevention.[22] Aspirin also suppresses cytokine production by leucocytes and endothelial cells.[23] In a double blind, placebo controlled, cross over trial in patients with proven coronary artery disease, aspirin (in a dose of 300 mg daily) reduced the production of interleukin 6 by 37% and CRP by 29%.[24] Similarly, other acute interventions shown to reduce mortality after acute myocardial infarction also suppress cytokine production. For example, intravenous magnesium given during myocardial infarction lowers peak serum interleukin 6 and matrix metalloproteinase 1 concentrations.[25] Angiotensin converting enzyme inhibitors reduce early mortality after acute infarction before their predicted beneficial effects on ventricular remodelling should appear.[26] These drugs suppress cytokine and TNF production and can be considered to have anti-inflammatory effects.[27] Corticosteroids, which are the drugs most widely used in medicine to suppress inflammation, have only been studied in the prethrombolytic era with inconsistent results. There is evidence that methylprednisolone reduces infarct size when given in the first few hours of infarction in both animal models and humans.[28–30] In the only large placebo controlled clinical trial of high dose intravenous methylprednisolone for acute myocardial infarction, although pericarditis was significantly reduced (7.5% *v* 18.5%),[31] overall mortality was unaffected.[32]

Conclusion

The reduction in case fatality of acute myocardial infarction by thrombolysis and aspirin cannot be caused by improved left ventricular function since this would be translated into a continuing benefit in the recovery period and beyond. The size of the acute inflammatory response triggered during infarction is proportional to the mortality from the event. There is clinical and experimental evidence of a reduction in the inflammatory response with these treatments and we postulate that this is the mechanism by which they reduce mortality. Further research into treatments aimed at reducing acute inflammation after myocardial infarction should be considered.

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IMAGES IN CARDIOLOGY

Coronary milking-like effect caused by systolic expansion of a traumatic focal left ventricular aneurysm

A 21 year old man was admitted to our centre with multiple fractures of the left femur, ribs, and hip following a car crash. On admission, the ECG showed elevation of the ST segment of 3–4 mm from V2 to V5. An increase in the MB fraction of creatinine kinase was detected. Due to the presence of cardiac tamponade, a pericardiocentesis was performed. Cardiac contusion was diagnosed. Seventy two hours later, the ECG abnormalities had improved and no Q waves were observed.

One week later the ECG showed a 2 mm ST segment depression in leads V4–V6. An echocardiogram revealed a focal left ventricular aneurysm (arrow; LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium.). An angiogram showed normal coronary arteries during the diastole (A) and occlusion of the intermediate artery in systole (B, arrow). This milking-like effect was ascribed to streching or compression of the artery during systolic expansion of the ventricular aneurysm. Since the patient's condition was poor and the cardiac complications did not cause haemodynamic instability, it was decided not perform an aneurysmectomy. It should be noted that the ventricular aneurysm was not irrigated by the narrowed coronary artery, which passed over this area. A bypass venous graft was not indicated since the myocardial damage was secondary to cardiac contusion. To reduce preload and facilitate the myocardial healing and remodelling, an angiotensin converting enzyme inhibitor was given. Acenocumarol was added to the treatment.

Eighteen months later, the ECG was normal and the echocardiogram showed persistence of the aneurysm. A thallium myocardial perfusion study revealed a focal myocardial defect in the anterolateral ventricular segment attributed to the aneurysm. No signs of myocardial ischaemia were detected.

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